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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/531,560	01/27/2006	Ian Alexander Shiels	38871.32	3534

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EXAMINER	
KHANNA, HEMANT	
ART UNIT	**PAPER NUMBER**
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,560	SHIELS ET AL.	
	Examiner	Art Unit	
	Hemant Khanna	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-20* is/are rejected.

7)☒ Claim(s) *13-14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of claims 1-15 in the reply filed on January 23, 2007 is acknowledged. The amendment to claims 2-15 and the addition of claims 16-20, is acknowledged. The Applicant states that claims 1-2, 6-20 read on the species "AcF-[OPdChaWR]". Because applicant did not distinctly and specifically point out the supposed errors in the election of species requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Applicant has elected the species of AcF-[OPdChaWR]. Applicant's species has not been found free of the prior art and is rejected under 35 USC 102(b) as set forth below.

Claims 1-20 are pending.

Claims 3-5 are being withdrawn from further consideration as being drawn to nonelected species, there being an allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 23, 2007.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) based on an application filed in Australia on October 16, 2002. It is noted that applicant has filed a certified copy of the 2002952086 application as required by 35 U.S.C. 119(b).

Claim Objections

3. Claim 13 is objected to because of the following informalities: the notation of numbers to represent compounds is unclear. For the benefit of clarity, Applicant is asked to refer to the notations with compound names or chemical formula's. Appropriate correction is required.

Claim 14 is objected to because of the following informalities: the notation of "described in PCT/AU02/01427" to denote the prior disclosure of compounds is improper. For the benefit of clarity, Applicant is asked to refer to the compound numbers with names or chemical formula's. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 recites the limitation "atleast the step". It is not clear whether the treatment method comprises an additional step not recited in the claim. It is not clear if the "atleast the step" is intended to limit the treatment method and what relationship is intended between the preamble and the additional method step. Thus claim 20 is indefinite.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 6-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, no that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the

claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co. the court stated:
"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In Gostelli, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention.

In the instant case, the claims are drawn to complement activation peptides.

(1) Level of skill and knowledge in the art:

The level of skill to practice the art of the instantly claimed invention is high with regard to method of treatment of cyclic peptides as inhibitors for G-protein coupled receptors for the treatment of osteoarthritis

(2) Partial structure:

Cyclic peptidomimitics of formula 1

(3) Physical and/or chemical properties:

Inhibitors of G-protein coupled receptors

(4) Functional characteristics:

Antagonist of G-protein coupled receptors having substantially no agonist activity

(5) Method of making the claimed invention:

Standard synthesis of the cyclic peptidomimetic compound

As stated supra, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim 1 is a broad generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to the class of cyclic peptidomimetics extensively modified with A, B, C, D, E, F and X^1. It must not be forgotten that the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. "MPEP § 2163. Here,

though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds represented by bulky substituents, bioisosteres, and side chains of any common or uncommon amino acids, beyond compounds disclosed in the examples in the specification. The specification describes AcF-[OpdChaWR] in the examples but the examples do not demonstrate any and all substituents that demonstrate the antagonism of a G-protein coupled receptor with substantially no agonist activity. While having written description for AcF-[OpdChaWR] identified in the specification, the specification is void of any cyclic peptidomimetics with functional characteristics that qualify as compounds being antagonists of G-protein coupled receptors. There is insufficient description of any and all substituents on the cyclic peptidomimetic that would allow one of skill in the art to practice the invention as claimed. The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.")

8. Claim 1-2, 6-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification, while being enabling for methods to treat osteoarthritis mediated via the C5a receptor utilizing a C5a receptor

antagonist, does not reasonably provide enablement for the methods to treat osteoarthritis mediated by any and all G-protein coupled receptors utilizing non-C5a receptor antagonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with claim 1.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Nature of the invention. The instant invention is to methods for treatment of osteoarthritis mediated by a G protein-coupled receptor in subjects by administering an inhibitor represented by the compound of formula I.

Breadth of the claims. According to the language of the claims, the scope of the method of treatment can be extrapolated to osteoarthritis mediated by any G-protein coupled receptor at all times in presence of the compound of formula I. The specification does not disclose a reasonable correlation between the treatment of osteoarthritis mediated by receptors other than the C5a receptor.

State and un/predictability of the prior art. The claimed subject matter is lacking in predictability. While examples in the art exist for the treatment of osteoarthritis, mediated via the C5a receptor, no examples or models exist for the treatment of osteoarthritis that are mediated by the broad class of G-protein coupled receptors, utilizing peptidomimetics, such as the compound of formula I. Specifically, Strachan (2000) teach that the immunoinflammatory response, such as rheumatoid arthritis has been associated with excessive levels of pro-inflammatory compounds C3a and C5a. However, only the C5a receptor antagonists have been shown to be effective in animal models of the disease (first paragraph, page 6560). The teachings of the prior art are being interpreted by the fact that there was no option for treating arthritis or other immuno-inflammatory conditions by intercepting a G-protein coupled receptor other than the C5a receptor. In view of the above teachings a person of skill in the art would have no evidence that treatment of osteoarthritis by a non-C5a receptor antagonist has any basis. It is presumed that the Applicant's intent is to treat osteoarthritis by inhibiting the

activity of C5aR with a peptidomimetic of formula I. Since the osteoarthritis is limited to being mediated by the C5a receptor, the inhibition of all G-protein coupled receptors for treatment, is not enabled.

Working examples. Although examples are disclosed in the specification that demonstrate the *in vivo* activity of AcF-[OPdChaWR] in a dog model of osteoarthritis, there is no evidence for the intended treatment of osteoarthritis by receptor antagonists non-specific to the G-protein coupled receptors that mediate osteoarthritis.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods to extrapolate the methods of treating osteoarthritis by the administration of a non-C5a receptor antagonist, from the method of treating osteoarthritis by the administration of a C5a specific receptor antagonist as represented by formula I. There is a lack of predictability in the art regarding the use of the claimed antagonist to antagonize receptors which are not C5a G-protein coupled receptors.

Amount of experimentation necessary. Given the unpredictability of the art in view of the use of the antagonist represented by formula I to treat osteoarthritis by antagonizing any G-protein coupled receptor, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate with the scope of the claim. Although the applicants have identified an interesting method of treatment of osteoarthritis, but essentially all of the work required to extrapolate the antagonism to any G-protein coupled receptor needs to be further undertaken.

Relative Skill of those skilled in the art. In view of the discussion of each of the preceding seven factors the level of skill in this art is high and is at least that of a Ph.D. with several years of experience in the art. As the cited art would point to, even with a level of skill in the art that is Ph.D. predictability of the results is not invariable.

In consideration of each of the factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-2, 6-20 rejected under 35 U.S.C. 102(b) as being anticipated by Woodruff (Arthritis & Rheumatism (Published Online 27 September 2002) 46: 2476-2485 as evidenced by Fairlie (WO 99/00406).

The claims are drawn to a method of treatment of osteoarthritis, comprising the step of administering an effective amount of AcF-[OPdChaWR] to a subject in need of such treatment.

Woodruff teach administering an effective amount of a peptidomimetic compound of formula 1 for the treatment of immune-mediated monarticular arthritis (abstract) wherein A is NH-acyl, B is the side chain of L-Phenylalanine, C is the side chain of L-Proline, D is the side chain of D-cyclohexylalanine, E is the side chain of L-tryptophan, F is the side chain of L-arginine, and X is $-(CH_2)_nNH-$, where n is 3; ((AcF-[OPdChaWR]), abstract left column, paragraph 4, page 2477), thus meeting the limitations of claims 1-2, 6-9, 13-14, 16-20. Woodruff also teach that the cyclic peptide AcF-[OPdChaWR] is a potent antagonist of human and rat C5a receptors on polymorphonuclear leukocytes (PMN's, left column, paragraph 4, page 2477), thus meeting the limitations of claim 10. Further Woodruff teach a combination therapy of the cyclic peptide with ibuprofen, thus meeting the limitations of claim 15. Further, as evidenced by Fairlie, the cyclic analog of AcF-[OpdChaWR] has a C5aR affinity of 0.3 μM (Table 6, page 42), thus meeting all the limitations of claims 11, and 12.

To the extent that the Applicant has employed rats with a reverse passive Arthus reaction or populations with a right knee joint swelling (Example 2) or dogs with reduced synovial fibrosis (Example 3) as indicative of an osteoarthritic population that can benefit from the administration of a C5aR antagonist, the population of arthritic rats having synovial fibrosis and proliferation (right column, paragraph 2, page 2482) or a population of rats having knee swelling (right column, Results, page 2478) as taught by Woodruff is encompassed within the population of patients who will benefit from the administration of the C5aR receptor antagonist AcF-[OpdChaWR]. Sufficient evidence of similarity is deemed to be present between the method of Woodruff and the

Applicant's claimed method to shift the burden to the Applicant to provide evidence that the claimed method is unobviously different than that of Woodruff.

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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April 04, 2007

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